Journal of Alzheimer's Disease 78 (2020) 1129–1136
DOI 10.3233/JAD-200124
IOS Press

PET Amyloid and Tau Status Are Differently Affected by Patient Features

Meng-Shan Tan[a], Yu-Xiang Yang[b], Hui-Fu Wang[a], Wei Xu[a], Chen-Chen Tan[a], Chuan-Tao Zuo[c], Qiang Dong[b], Lan Tan[a] and Jin-Tai Yu[b,*], Alzheimer's Disease Neuroimaging Initiative[1]
[a]*Department of Neurology, Qingdao Municipal Hospital, Qingdao University, Qingdao, China*
[b]*Department of Neurology and Institute of Neurology, Huashan Hospital, Shanghai Medical College, Fudan University, Shanghai, China*
[c]*PET Center, Huashan Hospital, Fudan University, Shanghai, China*

Handling Associate Editor: Yong Liu

Accepted 11 September 2020

Abstract.
Background: Amyloid-β (Aβ) plaques and tau neurofibrillary tangles are two neuropathological hallmarks of Alzheimer's disease (AD), which both can be visualized *in vivo* using PET radiotracers, opening new opportunities to study disease mechanisms.
Objective: Our study investigated 11 non-PET factors in 5 categories (including demographic, clinical, genetic, MRI, and cerebrospinal fluid (CSF) features) possibly affecting PET amyloid and tau status to explore the relationships between amyloid and tau pathology, and whether these features had a different association with amyloid and tau status.
Methods: We included 372 nondemented elderly from the Alzheimer's Disease Neuroimaging Initiative cohort. All underwent PET amyloid and tau analysis simultaneously, and were grouped into amyloid/tau quadrants based on previously established abnormality cut points. We examined the associations of above selected features with PET amyloid and tau status using a multivariable logistic regression model, then explored whether there was an obvious correlation between the significant features and PET amyloid or tau levels.
Results: Our results demonstrated that PET amyloid and tau status were differently affected by patient features, and CSF biomarker features provided most significant values associating PET findings. CSF $A\beta_{42/40}$ was the most important factor affecting amyloid PET status, and negatively correlated with amyloid PET levels. CSF pTau could significantly influence both amyloid and tau PET status. Besides CSF pTau and $A\beta_{42}$, *APOE* ε4 allele status and Mini-Mental State Examination scores also could influence tau PET status, and significantly correlated with tau PET levels.
Conclusion: Our results support that tau pathology possibly affected by Aβ-independent factors, implicating the importance of tau pathology in AD pathogenesis.

Keywords: Alzheimer's disease, amyloid-β, *APOE*, biomarker, cerebrospinal fluid, Mini-Mental State Examination, PET, tau

[1]Data used in preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (https://adni.loni.usc.edu). As such, the investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in analysis or writing of this report. A complete listing of ADNI investigators can be found at: https://adni.loni.usc.edu/wp-content/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf.

*Correspondence to: Prof. Jin-Tai Yu, MD, PhD, Department of Neurology and Institute of Neurology, Huashan Hospital, Shanghai Medical College, Fudan University, 12th Wulumuqi Zhong Road, Shanghai 200040, China. Tel.: +86 21 52888160; Fax:+86 21 62483421; E-mail: jintai_yu@fudan.edu.cn.

INTRODUCTION

Alzheimer disease (AD) pathology is characterized by cerebral plaques containing aggregates of amyloid-β (Aβ) peptides, as well as by neurofibrillary tangles containing hyperphosphorylated and aggregated tau [1, 2]. Although Aβ accumulation has been considered the initial insult that drives both the accumulation of tau pathology and tau-mediated neurodegeneration in AD, striking evidences indicate that tau pathology can progress also in an Aβ-independent manner [3]. Recently, the development of radiotracers binding to amyloid and tau allows the visualization and quantification of AD pathology in living patients using positron emission tomography (PET) [4], opening new opportunities to study disease mechanisms by exploring their relationships, and whether affected by the same or different factors.

Because tau PET imaging is a relatively novel technique, most previous studies have investigated the predictive power of demographic, clinical, Apolipoprotein E (*APOE*) genotype, magnetic resonance imaging (MRI) and cerebrospinal fluid (CSF) features for amyloid PET positivity [5, 6]. Particularly, a combination of demographic information, *APOE* ε4 carrier status, and neuropsychological tests are effective in predicting amyloid status. Meanwhile, CSF $A\beta_{42}$ and phosphorylated tau (pTau) have been shown to be predictive of amyloid PET status [5, 7, 8]. Indeed, current studies have also demonstrated the associations of CSF tau measures, *APOE* ε4 status with tau PET [9–11].

Large research cohorts with both amyloid and tau PET data have recently come into existence [12–14], and begun to investigate whether the association of selected patient features (including demographic, clinical, genetic, MRI, and CSF information) with amyloid and tau pathology differs when simultaneously detected by PET. In this exploratory study, we comprehensively investigate this information from the Alzheimer's Disease Neuroimaging Initiative (ADNI) cohort to explore the relationships between amyloid and tau pathology using PET data, and whether the above features had a different association with PET amyloid and tau status.

METHODS

Study design and participants

Data used in this study were obtained from ADNI database (https://adni.loni.usc.edu), and downloaded in November 2019. ADNI was launched in 2003 as a public-private partnership, led by Principal Investigator Michael W. Weiner, MD, VA Medical Center and University of California-San Francisco. For up-to-date information on ADNI, see https://www.adni-info.org. Our analyses included all nondemented elderly individuals with diagnosed mild cognitive impairment (MCI), subjective cognitive decline, and normal cognition, with clinical information, neuropsychological assessments, *APOE* ε4 carrier status, and AD-related CSF, MRI, and PET data. Most individuals only had the above data information at a certain time point. If there were multiple timepoint measurements, we retained the timepoint with the smallest amount of missing data. In total, 372 nondemented elderly individuals with both amyloid and tau PET data were included in our study (Fig. 1), and they were grouped into amyloid/tau quadrants based on previously established abnormality cut points (Fig. 2).

CSF measurements

CSF $A\beta_{42}$, $A\beta_{40}$, pTau, and tau were measured at the ADNI Biomarker Core Laboratory (Perelman School of Medicine University of Pennsylvania) using the automated Roche Elecsys and cobas e 601 immunoassay analyzer system. All CSF biomarker assays were performed in duplicate and averaged.

Structural MRI data

Hippocampal volume (HV) and estimated intracranial volume (eICV) were performed from T1-weighted MRI acquired with a Siemens Trio 3.0T or 1.5T scanner. Regional volume estimates were processed using the Freesurfer software (https://surfer.nmr.mgh.harvard.edu). HV was adjusted for eICV using the following equation: Adjusted HV (HVa) = Raw HV–b (eICV–Mean eICV), where b is the regression coefficient when HV is regressed against eICV.

PET data acquisition and analyses

A detailed description of PET image acquisition and processing can be found at https://adni.loni.usc.edu/datasamples/pet/. The AV45-PET (amyloid PET) and AV1415-PET (tau PET) standardized uptake value ratios (SUVRs) were formed by normalizing composite multi-region target regions of interest

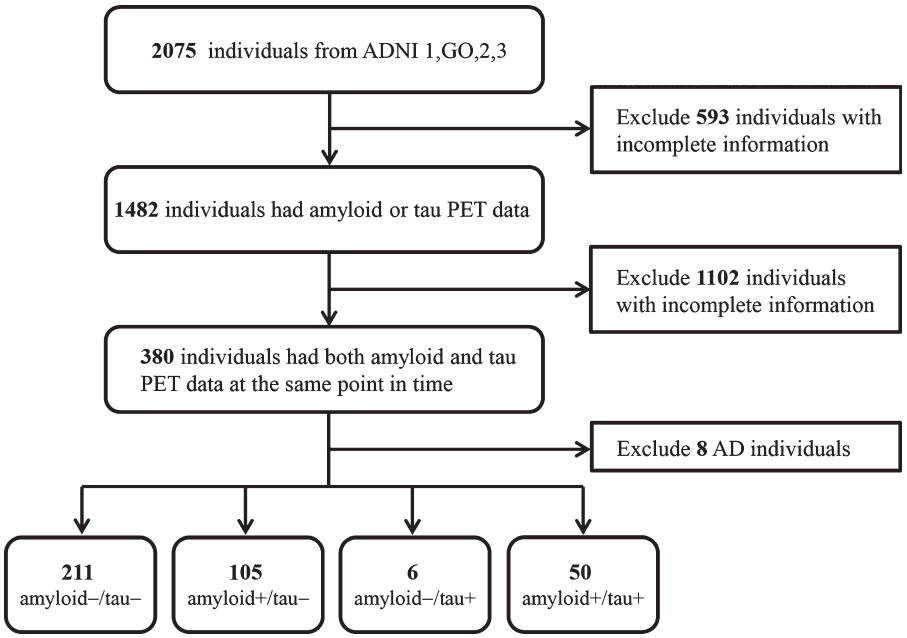

Fig. 1. Flow chart of study participants in ADNI. In total, 372 nondemented elderly individuals with both amyloid and tau PET data were included in our study, and grouped by previously established amyloid and tau PET cut points.

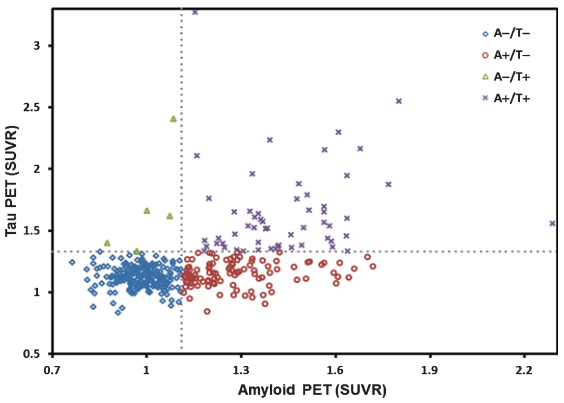

Fig. 2. The bivariate amyloid and tau PET distribution. Individuals were grouped into amyloid (A)/tau (T) quadrants based on previously established abnormality cut points of standardized uptake value ratio 1.1 (A) and 1.33 (T).

(ROIs) to the cerebellar crus gray matter. The amyloid PET target meta-ROI included the frontal, temporal, parietal, anterior cingulate, posterior cingulate, and precuneus [15]. The tau PET target meta-ROI included the amygdala, entorhinal cortex, fusiform, parahippocampal, and inferior temporal and middle temporal gyri [16]. The amyloid PET cut point denoting normal (A−) or abnormal (*A*+) was the SUVR value of 1.1. For tau PET, the cut point denoting normal (T−) or abnormal (T+) was the SUVR value of 1.33 [17].

Statistical analyses

Statistical analyses were conducted using R statistical software. Clinical and demographic characteristics for each variant were compared using *t* tests, F tests, chi-squared tests, or Wilcoxon rank-sum tests, as appropriate. First, we selected demographic information (age, gender, education), *APOE* ε4 carrier status, cognitive measures (Mini-Mental State Examination (MMSE) and Alzheimer Disease Assessment Scale–cognitive subscale 11 score), MRI HVa, and CSF biomarkers (CSF $A\beta_{42}$, $A\beta_{42/40}$, pTau, tau) as the possible influence factors for PET amyloid and tau status. We examined the associations of above selected features with PET amyloid and tau status using a multivariable logistic regression model, with either PET amyloid or tau positivity as the outcome. Then, we further explored whether there was an obvious correlation between the significant features and PET amyloid or tau levels, where PET amyloid and tau values were shown in the form of continuous variables.

Table 1
Demographic and clinical characteristics of study participants grouped by amyloid (A)/tau (T) PET status

	A−T−	A+T−	A−T+	A+T+
Demographics				
N (%)	211 (56.72)	105 (28.23)	6 (1.61)	50 (13.44)
Age, y (mean (SD))	70.33 (6.16)	73.72 (6.59)	68.47 (5.86)	71.98 (6.63)
Gender, male (%)	102 (48.34)	60 (57.14)	3 (50.00)	23 (46.00)
Education, y (median [IQR])	16.50 [15.00, 18.00]	17.00 [14.50, 19.00]	18.00 [14.00, 18.50]	16.00 [14.00, 18.00]
MMSE (mean (SD))	28.99 (1.33)	28.07 (2.39)	24.83 (5.31)	24.89 (4.79)
ADAS-cog (mean (SD))	7.67 (4.64)	9.96 (7.36)	10.80 (8.41)	12.61 (8.33)
Biomarkers				
APOE ε4 (0/1/2 alleles)	162/43/6	61/35/9	3/1/2	17/22/11
CSF $A\beta_{42}$, pg/mL (median [IQR])	1353.00 [948.90, 1824.00]	787.20 [544.05, 1037.50]	652.60 [486.15, 827.70]	642.60 [464.60, 755.05]
CSF $A\beta_{40}$, pg/mL (median [IQR])	18460.00 [15015.00, 23100.00]	19050.00 [15315.00, 23710.00]	20195 [12617.50, 24300.00]	18080.00 [15340.00, 24160.00]
CSF $A\beta_{42/40}$ (median [IQR])	0.083 [0.061, 0.092]	0.040 [0.033, 0.050]	0.031 [0.026, 0.043]	0.032 [0.026, 0.039]
CSF pTau, pg/mL (median [IQR])	18.20 [14.59, 22.66]	26.07 [20.08, 33.49]	41.59 [24.47, 51.74]	39.59 [26.30, 51.87]
CSF tau, pg/mL (median [IQR])	212.30 [170.15, 272.70]	284.30 [238.80, 346.50]	432.10 [238.50, 505.90]	401.00 [268.90, 478.90]
MRI HVa, mm^3 (median [IQR])	7235.01 [6403.68, 7976.23]	6861.15 [6092.54, 7518.19]	6684.46 [5812.44, 7497.02]	6633.73 [5753.39, 7572.71]
Amyloid PET, SUVR (median [IQR])	0.98 [0.93, 1.03]	1.26 [1.16, 1.36]	0.99 [0.95, 1.08]	1.41 [1.30, 1.57]
Tau PET, SUVR (median [IQR])	1.12 [1.07, 1.18]	1.15 [1.09, 1.22]	1.51 [1.33, 1.85]	1.53 [1.37, 1.76]
Syndrome diagnosis (%)				
NC	84 (39.81)	43 (40.95)	3 (50.00)	9 (18.00)
SCD	60 (28.44)	31 (29.52)	0 (0.00)	4 (8.00)
MCI	67 (31.75)	31 (29.52)	3 (50.00)	37 (74.00)

ADAS-cog, Alzheimer Disease Assessment Scale–cognitive subscale 11; HVa, adjusted Hippocampal volume; IQR, interquartile range; MCI, mild cognitive impairment; MMSE, Mini-Mental State Exam scores; N, number; NC, normal cognition; SCD, subjective cognitive decline; SD, standard deviation.

RESULTS

Participants with the bivariate amyloid and tau PET distribution

Totally, 372 nondemented elderly individuals with both amyloid and tau PET data were included in our study (Fig. 1). We segregated the bivariate distribution into four quadrants (Fig. 2) by previously established amyloid and tau PET cut points: normal amyloid and normal tau (A−T−), abnormal amyloid and normal tau (A + T−), normal amyloid and abnormal tau (A−T+), and abnormal amyloid and abnormal tau (A + T+). Fewer individuals (A−T+) were in the upper left quadrant. The detailed demographic and clinical characteristics of each group were summarized in Table 1. Using established cut points, in the A−T+and A + T+groups, most individuals (50.00% and 64.91%, respectively) were clinically diagnosed with MCI. The MMSE score were significantly reduced in the A−T+ and A + T+groups ($p < 0.001$). No significant differences in MMSE score were detected between A−T− versus A + T− group. As expected, the *APOE* ε4 allele frequency and CSF biomarker (CSF $A\beta_{42}$, $A\beta_{42/40}$, pTau, tau) levels were also significantly different between these groups ($p < 0.001$).

Variables affecting PET amyloid and tau status

We examined the associations of the selected features (including demographic, clinical, genetic, MRI, and CSF information) with PET amyloid and tau status using a multivariable logistic regression model (Fig. 3), trying to explore whether the above features had a different association with PET amyloid and tau status. Our results demonstrated that CSF $A\beta_{42/40}$ was significantly associated with amyloid PET status (OR = 0.575 [0.460–0.719], $p < 0.001$). CSF pTau could significantly influence both amyloid and tau PET status (OR = 1.468 [1.086–1.985], $p = 0.015$; OR = 2.848 [1.805–4.475], $p < 0.001$). Besides CSF pTau and $A\beta_{42}$, *APOE* ε4 allele status and MMSE scores also could influence tau PET status (OR = 2.037 [1.199–3.462], $p = 0.031$; OR = 0.728 [0.582–0.912], $p = 0.009$). Interestingly, tau PET levels were still a factor affecting amyloid PET status (OR = 1.471 [1.071–2.021], $p = 0.018$).

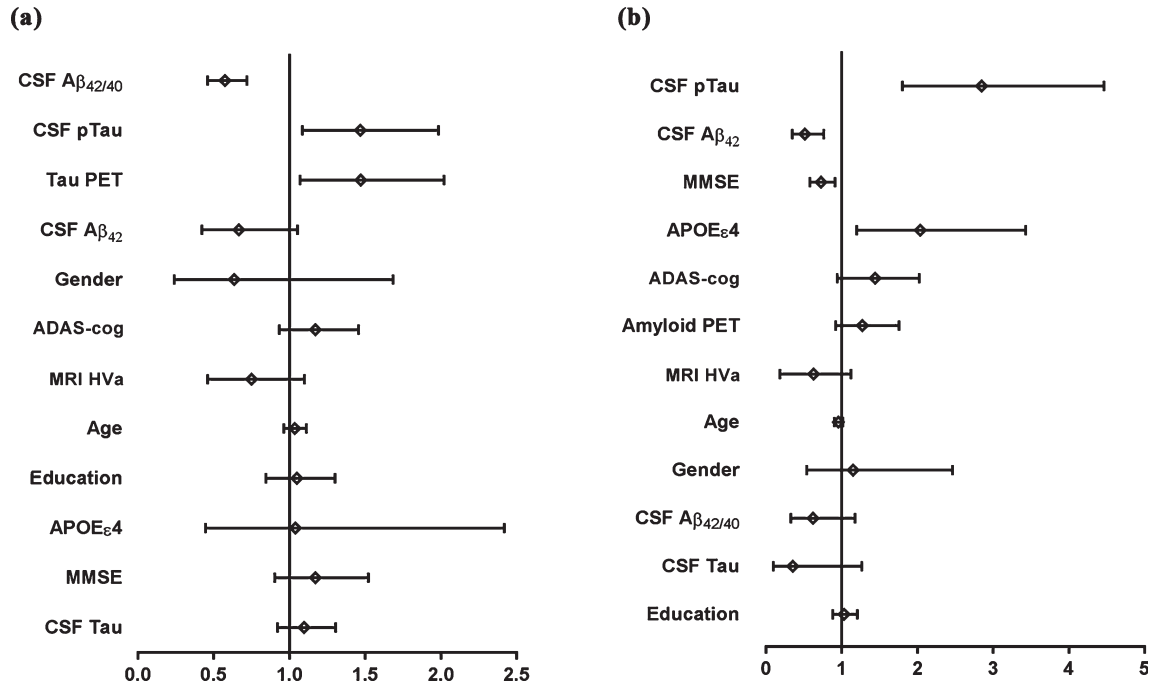

Fig. 3. The associations of patient features with PET amyloid and tau status. The associations of these patient features with (a) amyloid PET status and (b) tau PET status was explored by a multivariable logistic regression model. Odd ratio (OR) values with 95% confidence interval (CI) were calculated.

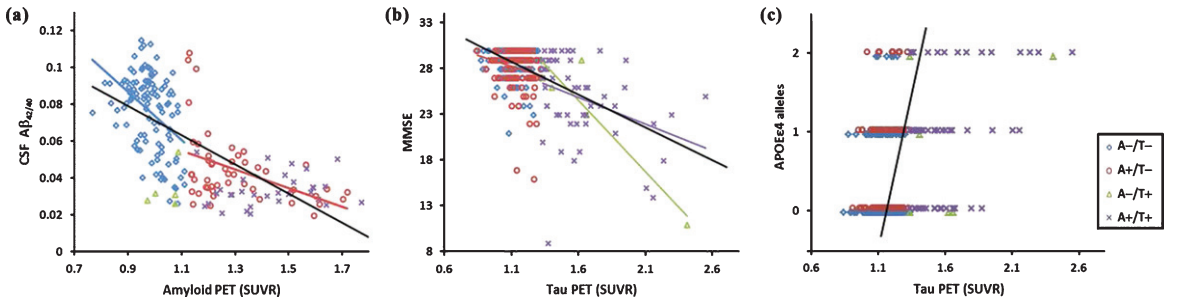

Fig. 4. The correlation analysis between the significant patient features and PET amyloid or tau levels. (a) CSF $A\beta_{42/40}$ was significantly and negatively correlated with amyloid PET levels ($r = -0.680$, $p < 0.01$). CSF $A\beta_{42/40}$ was also significantly and negatively correlated with amyloid PET levels in A−/T− subgroup ($r = -0.420$, $p < 0.01$), and in $A+$/T− subgroup ($r = -0.447$, $p < 0.01$). (b) MMSE score was significantly and negatively correlated with tau PET levels ($r = -0.557$, $p < 0.01$). MMSE score was also significantly and negatively correlated with tau PET levels in $A+$/T+subgroup ($r = -0.356$, $p < 0.01$), and in A−/T+subgroup ($r = -0.934$, $p < 0.01$). (c) There was statistically significant relationship between *APOE* ε4 allele status and tau PET levels ($r_s = 0.246$, $p < 0.01$). The regression lines were shown.

Correlation analysis with PET amyloid and tau levels

We performed correlation analysis to explore the relationships between the significant patient features and PET amyloid or tau levels, where the expression levels of amyloid and tau PET SUVR values were shown in the form of continuous variables. Our results revealed that CSF $A\beta_{42/40}$ was significantly and negatively correlated with amyloid PET levels ($r = -0.680$, $p < 0.01$; Fig. 4a); while, MMSE score negatively correlated with tau PET levels ($r = -0.557$, $p < 0.01$; Fig. 4b) using Pearson's correlation. There was also statistically significant

relationship between *APOE* ε4 allele status and tau PET levels ($r_s = 0.246$, $P < 0.01$; Fig. 4c) using Spearman's rank correlation.

DISCUSSION

We investigated the possible factors of patient features (including demographic, clinical, genetic, MRI, and CSF information) affecting amyloid and tau status based on PET data to explore the relationships between amyloid and tau pathology, and whether these features had a different association with amyloid and tau status. Our results demonstrated that PET amyloid and tau status were differently affected by the patient features. For example, CSF $A\beta_{42/40}$ was the most important factor affecting amyloid PET status, and there was a significant negative correlation between their expression levels. CSF pTau could significantly influence both amyloid and tau PET status. Besides CSF pTau and $A\beta_{42}$, *APOE* ε4 allele status and MMSE scores also could influence tau PET status, and significantly correlated with tau PET levels.

The idea to study differences in the influence of patient features on amyloid and tau pathology was based on the theory that Aβ and tau pathology might be induced through correlated yet independent pathways [3]. Although a longstanding amyloid hypothesis implicates Aβ as the initiator and driver of tau pathology and tau-mediated neurodegeneration in AD pathogenesis, striking evidences indicate that tau pathology can progress in an Aβ-independent manner [3]. In addition, the failure of several anti-amyloid therapies to improve clinical symptoms in AD dementia [18] also highlights an urgency to understand the relationships between Aβ and tau, and their influence factors in AD progression.

As expected, CSF $A\beta_{42/40}$ ratio is superior to $A\beta_{42}$ alone as an important factor for amyloid-positivity by PET, which might be explained by the fact that the ratio compensates for general between-individual variations in CSF total Aβ concentrations [19]. And there is a growing body of evidence that suggests the better diagnostic performance of the CSF $A\beta_{42/40}$ ratio compared to CSF $A\beta_{42}$ alone [20]. Consistent with previous studies [5, 8], CSF pTau has also been shown to be associated with amyloid PET status. Interestingly, tau PET levels are still a factor affecting amyloid PET status in our current study. Those results suggest that interactions between amyloid and tau might be cyclic in nature. Previous observations have pointed out that overexpression of human tau in APP transgenic mice can increase Aβ deposition [21, 22], tau immunization can reduce Aβ plaque burden [23], and exogenous extracellular tau could increase Aβ production *in vitro* [21].

As for tau PET, our result indicates that CSF pTau is the most important factor affecting tau PET status, and the second factor is CSF $A\beta_{42}$. The close relationship between tau PET and CSF pTau is in line with the recently updated research framework [24] that considers tau PET and CSF pTau as the relevant tauopathy biomarkers to classify individuals. Besides CSF pTau and $A\beta_{42}$ (both the key factor affecting amyloid and tau PET status [8, 9]), *APOE* ε4 allele status and MMSE scores could influence tau PET status, and significantly correlated with tau PET levels in our current study. This is supported by the data showing that *APOE* ε4 has been implicated in numerous processes independent of Aβ in preclinical models of AD [25, 26]; and *APOE* ε4 also as a contributor to tauopathy, independent of age and Aβ [11]. Interestingly, accumulating evidence also suggests that CSF pTau may increase in an early disease stage, whereas increased tau PET signal might reflect the overall accumulation of pathology in brain, which correlated with the subsequent brain atrophy [27], the lower MMSE score [9], and decreased cognitive performance [28].

These data above support disease models in which tau pathology possibly affected by Aβ-independent factors, implicating the importance of tau pathology in AD pathogenesis. Because of tau PET, but not amyloid PET, are associated with the severity of patient's cognitive deficits (especially MMSE score), tau PET could be useful for the design of clinical trials and could increase the ability to detect a treatment effect. Future investigations will be needed to include more patient features as possible influencing factors, and try to explore additional Aβ-independent factors for tau pathology to further our understanding of the complex mechanisms underlying neurodegeneration in AD. Meanwhile, with the wide application of tau PET, future longitudinal studies would enable a more precise characterization of AD biomarker trajectories.

Our study had some limitations. The number of individuals within each group was relatively small, and there were differences in the proportion of the sample size among these groups. In addition, a single cutoff point approach lacks accuracy when research questions require high diagnostic certainty. Reproducibility of findings in different patient groups from different centers would provide more statistically powerful results in future.

In summary, our results illustrate that PET amyloid and tau status are differently affected by patient features. In this exploratory study, tau PET is affected by Aβ-independent factors, and more relevant to patient's cognitive performance, which implicating the importance of tau pathology, and tau as a relevant target for disease-modifying therapy.

ACKNOWLEDGMENTS

This work was also supported by grants from the National Natural Science Foundation of China (91849126), the National Key R&D Program of China (2018YFC1314700), Taishan Scholars Program of Shandong Province (tsqn20161078), Shanghai Municipal Science and Technology Major Project (No.2018SHZDZX01) and ZHANGJIANG LAB, Tianqiao and Chrissy Chen Institute, and the State Key Laboratory of Neurobiology and Frontiers Center for Brain Science of Ministry of Education, Fudan University.

Data collection and sharing was funded by ADNI. ADNI is funded by the National Institute on Aging, the National Institute of Biomedical Imaging and Bioengineering, and through generous contributions from the following: Alzheimers Association; Alzheimers Drug Discovery Foundation; BioClinica, Inc.; Biogen Idec Inc.; Bristol-Myers Squibb Company; Eisai Inc.; Elan Pharmaceuticals, Inc.; Eli Lilly and Company; F. Hoffmann-La Roche Ltd and its affiliated company Genentech, Inc.; GE Healthcare; Innogenetics, N.V.; IXICO Ltd.; Janssen Alzheimer Immunotherapy Research & Development, LLC.; Johnson & Johnson Pharmaceutical Research & Development LLC.; Medpace, Inc.; Merck & Co., Inc.; Meso Scale Diagnostics, LLC.; NeuroRx Research; Novartis Pharmaceuticals Corporation; Pfizer Inc.; Piramal Imaging; Servier; Synarc Inc.; and Takeda Pharmaceutical Company. The Canadian Institutes of Health Research is providing funds to support ADNI clinical sites in Canada. Private sector contributions are facilitated by the Foundation for the National Institutes of Health (https://www.fnih.org). The grantee organization is the Northern California Institute for Research and Education, and the study is coordinated by the Alzheimer's Disease Cooperative Study at the University of California, San Diego. ADNI data are disseminated by the Laboratory for Neuro Imaging at the University of Southern California.

Authors' disclosures available online (https://www.j-alz.com/manuscript-disclosures/20-0124r3).

REFERENCES

[1] Hardy J, Allsop D (1991) Amyloid deposition as the central event in the aetiology of Alzheimer's disease. *Trends Pharmacol Sci* **12**, 383-388.

[2] Selkoe DJ (1991) The molecular pathology of Alzheimer's disease. *Neuron* **6**, 487-498.

[3] van der Kant R, Goldstein LSB, Ossenkoppele R (2020) Amyloid-beta-independent regulators of tau pathology in Alzheimer disease. *Nat Rev Neurosci* **21**, 21-35.

[4] Chandra A, Valkimadi PE, Pagano G, Cousins O, Dervenoulas G, Politis M (2019) Applications of amyloid, tau, and neuroinflammation PET imaging to Alzheimer's disease and mild cognitive impairment. *Hum Brain Mapp* **40**, 5424-5442.

[5] Reimand J, de Wilde A, Teunissen CE, Zwan M, Windhorst AD, Boellaard R, Barkhof F, van der Flier WM, Scheltens P, van Berckel BNM, Ossenkoppele R, Bouwman F (2019) PET and CSF amyloid-beta status are differently predicted by patient features: Information from discordant cases. *Alzheimers Res Ther* **11**, 100.

[6] Mielke MM, Wiste HJ, Weigand SD, Knopman DS, Lowe VJ, Roberts RO, Geda YE, Swenson-Dravis DM, Boeve BF, Senjem ML, Vemuri P, Petersen RC, Jack CR, Jr (2012) Indicators of amyloid burden in a population-based study of cognitively normal elderly. *Neurology* **79**, 1570-1577.

[7] Li QX, Villemagne VL, Doecke JD, Rembach A, Sarros S, Varghese S, McGlade A, Laughton KM, Pertile KK, Fowler CJ, Rumble RL, Trounson BO, Taddei K, Rainey-Smith SR, Laws SM, Robertson JS, Evered LA, Silbert B, Ellis KA, Rowe CC, Macaulay SL, Darby D, Martins RN, Ames D, Masters CL, Collins S (2015) Alzheimer's disease normative cerebrospinal fluid biomarkers validated in PET amyloid-beta characterized subjects from the Australian Imaging, Biomarkers and Lifestyle (AIBL) study. *J Alzheimers Dis* **48**, 175-187.

[8] Krance SH, Cogo-Moreira H, Rabin JS, Black SE, Swardfager W (2019) Reciprocal predictive relationships between amyloid and tau biomarkers in Alzheimer's disease progression: An empirical model. *J Neurosci* **39**, 7428-7437.

[9] La Joie R, Bejanin A, Fagan AM, Ayakta N, Baker SL, Bourakova V, Boxer AL, Cha J, Karydas A, Jerome G, Maass A, Mensing A, Miller ZA, O'Neil JP, Pham J, Rosen HJ, Tsai R, Visani AV, Miller BL, Jagust WJ, Rabinovici GD (2018) Associations between [(18)F]AV1451 tau PET and CSF measures of tau pathology in a clinical sample. *Neurology* **90**, e282-e290.

[10] Mattsson N, Scholl M, Strandberg O, Smith R, Palmqvist S, Insel PS, Hagerstrom D, Ohlsson T, Zetterberg H, Jogi J, Blennow K, Hansson O (2017) (18)F-AV-1451 and CSF T-tau and P-tau as biomarkers in Alzheimer's disease. *EMBO Mol Med* **9**, 1212-1223.

[11] Therriault J, Benedet AL, Pascoal TA, Mathotaarachchi S, Chamoun M, Savard M, Thomas E, Kang MS, Lussier F, Tissot C, Parsons M, Qureshi MNI, Vitali P, Massarweh G, Soucy JP, Rej S, Saha-Chaudhuri P, Gauthier S, Rosa-Neto P (2020) Association of Apolipoprotein E epsilon4 with medial temporal tau independent of amyloid-beta. *JAMA Neurol* **77**, 470-479.

[12] Betthauser TJ, Koscik RL, Jonaitis EM, Allison SL, Cody KA, Erickson CM, Rowley HA, Stone CK, Mueller KD, Clark LR, Carlsson CM, Chin NA, Asthana S, Christian BT, Johnson SC (2020) Amyloid and tau imaging biomarkers

explain cognitive decline from late middle-age. *Brain* **143**, 320-335.

[13] Brier MR, Gordon B, Friedrichsen K, McCarthy J, Stern A, Christensen J, Owen C, Aldea P, Su Y, Hassenstab J, Cairns NJ, Holtzman DM, Fagan AM, Morris JC, Benzinger TL, Ances BM (2016) Tau and Abeta imaging, CSF measures, and cognition in Alzheimer's disease. *Sci Transl Med* **8**, 338ra366.

[14] Hanseeuw BJ, Betensky RA, Jacobs HIL, Schultz AP, Sepulcre J, Becker JA, Cosio DMO, Farrell M, Quiroz YT, Mormino EC, Buckley RF, Papp KV, Amariglio RA, Dewachter I, Ivanoiu A, Huijbers W, Hedden T, Marshall GA, Chhatwal JP, Rentz DM, Sperling RA, Johnson K (2019) Association of amyloid and tau with cognition in preclinical Alzheimer disease: A longitudinal study. *JAMA Neurol* **76**, 915-924.

[15] Joshi AD, Pontecorvo MJ, Clark CM, Carpenter AP, Jennings DL, Sadowsky CH, Adler LP, Kovnat KD, Seibyl JP, Arora A, Saha K, Burns JD, Lowrey MJ, Mintun MA, Skovronsky DM (2012) Performance characteristics of amyloid PET with florbetapir F 18 in patients with alzheimer's disease and cognitively normal subjects. *J Nucl Med* **53**, 378-384.

[16] Jack CR, Jr., Wiste HJ, Weigand SD, Therneau TM, Lowe VJ, Knopman DS, Gunter JL, Senjem ML, Jones DT, Kantarci K, Machulda MM, Mielke MM, Roberts RO, Vemuri P, Reyes DA, Petersen RC (2017) Defining imaging biomarker cut points for brain aging and Alzheimer's disease. *Alzheimers Dement* **13**, 205-216.

[17] Jack CR, Jr., Wiste HJ, Therneau TM, Weigand SD, Knopman DS, Mielke MM, Lowe VJ, Vemuri P, Machulda MM, Schwarz CG, Gunter JL, Senjem ML, Graff-Radford J, Jones DT, Roberts RO, Rocca WA, Petersen RC (2019) Associations of amyloid, tau, and neurodegeneration biomarker profiles with rates of memory decline among individuals without dementia. *JAMA* **321**, 2316-2325.

[18] Castello MA, Jeppson JD, Soriano S (2014) Moving beyond anti-amyloid therapy for the prevention and treatment of Alzheimer's disease. *BMC Neurol* **14**, 169.

[19] Lewczuk P, Matzen A, Blennow K, Parnetti L, Molinuevo JL, Eusebi P, Kornhuber J, Morris JC, Fagan AM (2017) Cerebrospinal fluid Abeta42/40 corresponds better than Abeta42 to amyloid PET in Alzheimer's disease. *J Alzheimers Dis* **55**, 813-822.

[20] Hansson O, Lehmann S, Otto M, Zetterberg H, Lewczuk P (2019) Advantages and disadvantages of the use of the CSF Amyloid beta (Abeta) 42/40 ratio in the diagnosis of Alzheimer's disease. *Alzheimers Res Ther* **11**, 34.

[21] Bright J, Hussain S, Dang V, Wright S, Cooper B, Byun T, Ramos C, Singh A, Parry G, Stagliano N, Griswold-Prenner I (2015) Human secreted tau increases amyloid-beta production. *Neurobiol Aging* **36**, 693-709.

[22] Jackson RJ, Rudinskiy N, Herrmann AG, Croft S, Kim JM, Petrova V, Ramos-Rodriguez JJ, Pitstick R, Wegmann S, Garcia-Alloza M, Carlson GA, Hyman BT, Spires-Jones TL (2016) Human tau increases amyloid beta plaque size but not amyloid beta-mediated synapse loss in a novel mouse model of Alzheimer's disease. *Eur J Neurosci* **44**, 3056-3066.

[23] Dai CL, Tung YC, Liu F, Gong CX, Iqbal K (2017) Tau passive immunization inhibits not only tau but also Abeta pathology. *Alzheimers Res Ther* **9**, 1.

[24] Jack CR, Jr., Bennett DA, Blennow K, Carrillo MC, Dunn B, Haeberlein SB, Holtzman DM, Jagust W, Jessen F, Karlawish J, Liu E, Molinuevo JL, Montine T, Phelps C, Rankin KP, Rowe CC, Scheltens P, Siemers E, Snyder HM, Sperling R (2018) NIA-AA Research Framework: Toward a biological definition of Alzheimer's disease. *Alzheimers Dement* **14**, 535-562.

[25] Shi Y, Yamada K, Liddelow SA, Smith ST, Zhao L, Luo W, Tsai RM, Spina S, Grinberg LT, Rojas JC, Gallardo G, Wang K, Roh J, Robinson G, Finn MB, Jiang H, Sullivan PM, Baufeld C, Wood MW, Sutphen C, McCue L, Xiong C, Del-Aguila JL, Morris JC, Cruchaga C, Fagan AM, Miller BL, Boxer AL, Seeley WW, Butovsky O, Barres BA, Paul SM, Holtzman DM (2017) ApoE4 markedly exacerbates tau-mediated neurodegeneration in a mouse model of tauopathy. *Nature* **549**, 523-527.

[26] Zhao N, Liu CC, Qiao W, Bu G (2018) Apolipoprotein E, receptors, and modulation of Alzheimer's disease. *Biol Psychiatry* **83**, 347-357.

[27] La Joie R, Visani AV, Baker SL, Brown JA, Bourakova V, Cha J, Chaudhary K, Edwards L, Iaccarino L, Janabi M, Lesman-Segev OH, Miller ZA, Perry DC, O'Neil JP, Pham J, Rojas JC, Rosen HJ, Seeley WW, Tsai RM, Miller BL, Jagust WJ, Rabinovici GD (2020) Prospective longitudinal atrophy in Alzheimer's disease correlates with the intensity and topography of baseline tau-PET. *Sci Transl Med* **12**, eaau5732.

[28] Bejanin A, Schonhaut DR, La Joie R, Kramer JH, Baker SL, Sosa N, Ayakta N, Cantwell A, Janabi M, Lauriola M, O'Neil JP, Gorno-Tempini ML, Miller ZA, Rosen HJ, Miller BL, Jagust WJ, Rabinovici GD (2017) Tau pathology and neurodegeneration contribute to cognitive impairment in Alzheimer's disease. *Brain* **140**, 3286-3300.